

# Statistical analyses of hydrophobic interactions: A mini-review

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## Abstract

This review focuses on the striking recent progress in solving for hydrophobic interactions between small inert molecules. We discuss several new understandings. Firstly, the *inverse temperature* phenomenology of hydrophobic interactions, *i.e.*, strengthening of hydrophobic bonds with increasing temperature, is decisively exhibited by hydrophobic interactions between atomic-scale hard sphere solutes in water. Secondly, inclusion of attractive interactions associated with atomic-size hydrophobic reference cases leads to substantial, non-trivial corrections to reference results for purely repulsive solutes. Hydrophobic bonds are *weakened* by adding solute dispersion forces to treatment of reference cases. The classic statistical mechanical theory for those corrections is not accurate in this application, but molecular quasi-chemical theory shows promise. Finally, because of the masking roles of excluded volume and attractive interactions, comparisons that do not discriminate the different possibilities face an interpretive danger.

## Introduction

The molecular theory of hydrophobic effects,<sup>1</sup> and particularly of hydrophobic interactions,<sup>2</sup> has been a distinct intellectual challenge for many decades. The intellectual challenge originates with the entropy-driven character of hydrophobic interactions.<sup>3–5</sup> Explanation of those entropies requires molecular statistical mechanics. Statistical mechanical theories of hydrophobic effects have been rare, difficult, and unconvincing in their inceptions,<sup>1,6</sup> especially in contrast to the voluminous and graphic results from molecular simulations of aqueous solutions of hydrophobic species.

It is correct and traditional to introduce work on hydrophobic effects by calling-out their vast importance.<sup>7</sup> But the subject is so vast that the traditional calling-out scarcely ever does justice to the whole. We submit to that situation and pattern here, giving a few examples, and citations of dis-

cussions more extended than would fit in this mini-review. Hydrophobic effects can play a prominent role in practical materials science associated with aqueous solution interfaces.<sup>8–13</sup> Work on clathrate hydrates, in which molecular cages of water trap gases,<sup>14,15</sup> provides an example pertinent to energy applications. More traditional yet is work on biomolecular structure,<sup>16,17</sup> and even more expansive discussions are associated with the origins of life.<sup>18,19</sup> We note that an immediate precedent of this work offered a focused discussion of the expression of hydrophobic interactions in aqueous polymer solutions,<sup>20</sup> and closely related work gave an extended discussion of theoretical work on atomic-scale hydrophobic interactions.<sup>21</sup>

The subjects of hydrophobic hydration and hydrophobic interactions are indeed vast, and this review is not exhaustive. Instead we focus on the recent interplay between statistical mechanical theory of hydrophobic interactions and simulation ex-

periments designed to test and clarify those theories.

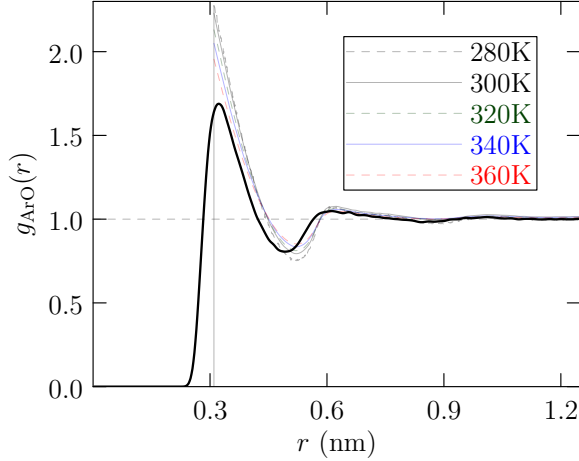


Figure 1: Radial distribution of water O atoms from a dissolved Ar atom,  $T = 300$  K,  $p = 1$  atm (heavy curve). Radial distributions (fainter, background curves) for hard-sphere model solutes with distances of closest approach,  $\lambda = 0.31$  nm, on the basis of cavity methods.<sup>22–24</sup>

The distinction of hydrophobic interactions from hydrophobic hydration is important and well-recognized, but deserves emphasis. Hydrophobic interactions are free energy changes resulting from the mutual positioning of hydrophobic species in water. In contrast, hydrophobic hydration addresses the placement of the water molecules neighboring hydrophobic species in water. An example of a hydrophobic hydration characteristic is the radial distribution,  $g_{\text{ArO}}(r)$ , of water oxygen (O) atoms near an argon (Ar) atom solute in water (FIG. 1). This shows crowding of water near that hydrophobic solute. Water structures similarly around other gases, including hydrogen<sup>25–28</sup> and even carbon dioxide.<sup>29</sup> Hydrophobic interactions and hydrophobic hydration phenomena are expected to be fundamentally related. But they have shown distinctly different variabilities, and theories of hydrophobic hydration<sup>30</sup> have gone further than theories of hydrophobic interactions.

Another hydrophobic hydration characteristic, and one for which there is well-developed statistical mechanical theory, is the dependence of the contact value of the hard-sphere radial distribution functions (FIG. 1) on the distance,  $\lambda$ , of closest approach of a water O atom (FIG. 2). The max-

imum of  $G(\lambda)$  in FIG. 2 provides an unambiguous separation of large and small  $\lambda$  regimes. Here that boundary is near  $\lambda = 0.3$  nm.  $G(\lambda)$  supplies the compressive force exerted by the water on a hard cavity.<sup>31</sup> By falling in the neighborhood of that maximum, the results of FIG. 1 demonstrate the case of the *strongest compressive force* on a hydrophobic spherical exclusion. The results (FIG. 2) also draw a clear distinction between solvation structuring of *n*-hexane, a typical organic solvent, and liquid water.

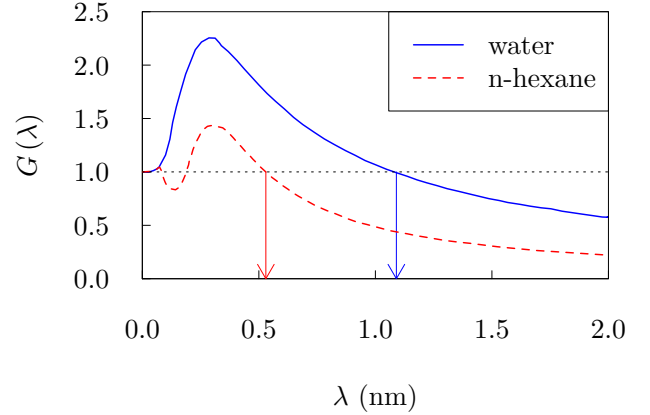


Figure 2: For a hard sphere in water and *n*-hexane, contact values of radial distribution of O (water) or C (*n*-hexane) from application of the revised scaled-particle model. Results for  $T = 270$  K along the saturation curves of water and hexane, redrawn from Ref. 32. The maximum value for water, about 2.2, agrees with the radial distributions of FIG. 1 though the precise values of  $\lambda$  near 0.3 nm are slightly different. Both water and *n*-hexane cases show density depletion in the local neighborhood of the hard sphere for gradually larger  $\lambda$ , but this behavior is more advanced for *n*-hexane:  $G(\lambda) < 1$ , for  $\lambda > 0.53$  nm for *n*-hexane, and for  $\lambda > 1.09$  nm for water.

In contrast with hydrophobic hydration, the association (FIG. 3) of end-methyl groups capping a poly-ethylene-oxide (PEO) oligomer shows a distinct hydrophobic interaction.<sup>33,34</sup> That interaction is also suggested by the density profile of poly-dimethylsiloxane (PDMS) interacting with a solid surface.<sup>35</sup> The PEO example was constructed for feasible direct measurement, *e.g.*, by neutron diffraction, of the hydrophobic interactions shown. Preliminary experiments of that sort, studying

end-labeled PEO chains, are already available.<sup>24</sup> Simpler experimental studies of loop-closure<sup>36</sup> of PEO chains were later discussed as an extension of this idea.<sup>37</sup>

This review focuses on the striking recent progress in solving for these hydrophobic interactions between small inert molecules.<sup>20,22,39–41</sup> We anticipate discussion below by noting the new understandings. (1) The *inverse temperature* phenomenology of hydrophobic interactions, *i.e.*, strengthening of hydrophobic bonds with increasing temperature, is decisively exhibited by hydrophobic interactions between atomic-scale hard sphere solutes in water. (2) Inclusion of attractive interactions associated with atomic-size hydrophobic reference cases leads to substantial corrections to reference results for purely repulsive solutes. Hydrophobic bonds are *weakened* by adding solute dispersion forces to treatment of reference cases.<sup>20,42</sup> The classic statistical mechanical theory for those corrections is not accurate in this application,<sup>20,42</sup> but molecular quasi-chemical theory (QCT) shows promise.<sup>42</sup> (3) Theories, comparisons, models, or pictures that do not distinguish effects of reference (repulsive force) cases from those with interactions, including masking attractions, are not safe.<sup>43–45</sup>

In closing this Introduction, we point<sup>19,46,47</sup> to the most ambitious attempt to extract physical insight from the statistical mechanical theories that work for hydrophobic effects.<sup>48–51</sup> That analysis suggested that the equation of state of liquid water is the primary source of peculiarity of hydrophobic effects.<sup>19,47,51</sup> The compressibility of water is low, compared to organic solvents. Water is stiffer and that low compressibility is weakly sensitive to temperature along the vapor saturation curve. Similarly, the density of water changes unusually slowly along that vapor saturation curve. Good theories should faithfully incorporate those equation of state characteristics even if they compromise the molecular-scale description of hydration structure. This “equation of state” explanation of hydrophobic effects may not be fully sufficient on its own, but it is the most defensible picture currently available.

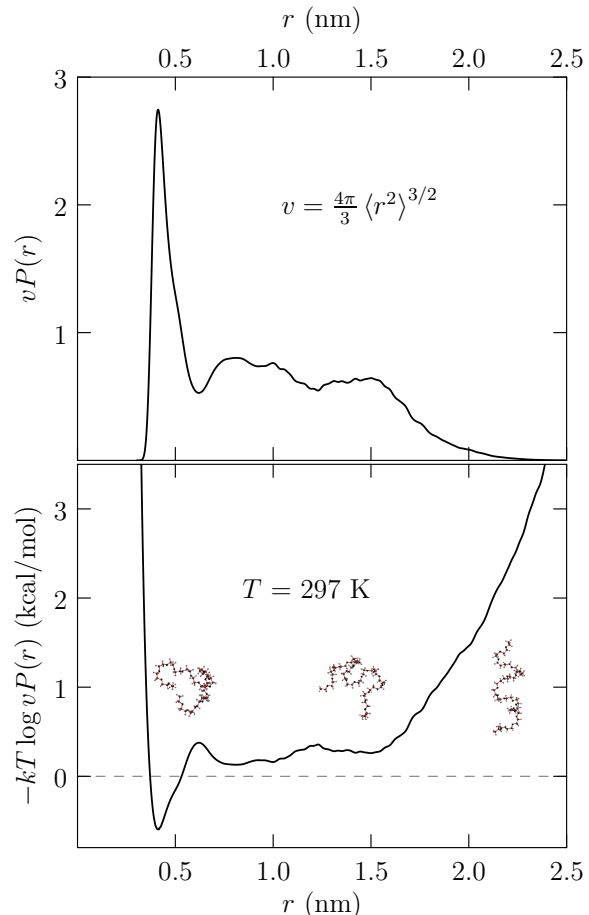


Figure 3: (upper) Probability density  $P(r)$  for methyl-methyl length for  $[\text{CH}_3(\text{CH}_2\text{-O-CH}_2)_m\text{CH}_3](\text{aq})$  with  $m = 21$ . The normalization is chosen in analogy with conventional atom-atom radial distribution functions of liquids. (lower) Potential of the average end-to-end forces showing distinct loop-closure, globule, and high-extension regions. The choice of normalization for the upper panel also sets the origin of the y-axis of the lower panel. Results for  $r < 1.0$  nm were obtained with the WHAM procedure.<sup>38</sup> Those high-resolution results were matched to observation of  $P(r)$  overall from parallel tempering molecular simulations.<sup>33</sup>

# Cavity Methods to Obtain Hydrophobic Interactions between Hard-spheres in Water

We first discuss hydrophobic interactions between hard-sphere solutes, A.<sup>22</sup> We consider the radial distribution function

$$g_{AA}(r) = \exp[-\beta u_{AA}(r)] y_{AA}(r) \quad (1)$$

for atomic-size hard spheres relying on the *cavity distribution function*,  $y_{AA}(r)$ , exploiting trial placements into the system volume (Fig. 4). We make  $n_t$  trial placements into the system volume  $V$  for each configuration sampled by the molecular simulation. Those placements are spatially uniform, and  $(n_t - 1)\Delta V/V$  should land in a volume  $\Delta V$ , which is a thin shell of radius  $r > 0$  surrounding a permissible insertion. The number of permissible placements obtained in the shell for each configuration is denoted by  $\Delta n_s(r)$ . Averaging over configurations, we estimate

$$\left(\frac{\bar{n}_s}{V}\right) y_{AA}(r) \Delta V = \Delta \bar{n}_s(r), \quad (2)$$

when  $n_t \rightarrow \infty$ . This is the same formula as if the permissible insertions were actual particles though they are not.

The radial distribution function  $g_{AA}(r) = y_{AA}(r)$  for  $r \geq 2 \times 0.17 \text{ nm} = 0.34 \text{ nm}$ , but is zero for  $r < 0.34 \text{ nm}$  (Fig. 5). The contact values,  $g_{AA}(r = 0.34 \text{ nm})$  obtained are more than twice larger than the predictions of the Pratt-Chandler (PC) theory.<sup>53</sup> The contact values are higher for higher temperatures, indicating stronger hydrophobic contact attractions at higher temperatures, agreeing with the results of Mancera, *et al.*, and preceding work discussed there.<sup>54</sup> The contact values of the PC theory also increase with  $T$  but those increases are small,<sup>53</sup> and the PC contact values are sufficiently different from these numerical values that the small increases are not interesting.

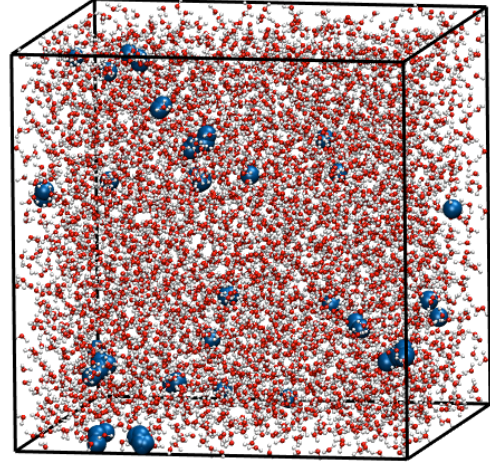


Figure 4: A configuration of  $5 \times 10^3$  water molecules together with the spherical inclusions identified by  $n_t = 2 \times 10^5$  trial placements of a hard sphere with distance of closest approach to an oxygen atom of 0.31 nm. This size corresponds approximately to A=Ar solute, for which the van der Waals length parameter  $\sigma_A$  is about 0.34 nm.<sup>52</sup> Thus, we adopt  $0.31 \text{ nm} - 0.17 \text{ nm} = 0.14 \text{ nm}$  as a van der Waals contact radius of the water oxygen atom. Hard sphere solutes of this size have about maximal O contact density (FIG. 2).<sup>32,51</sup>

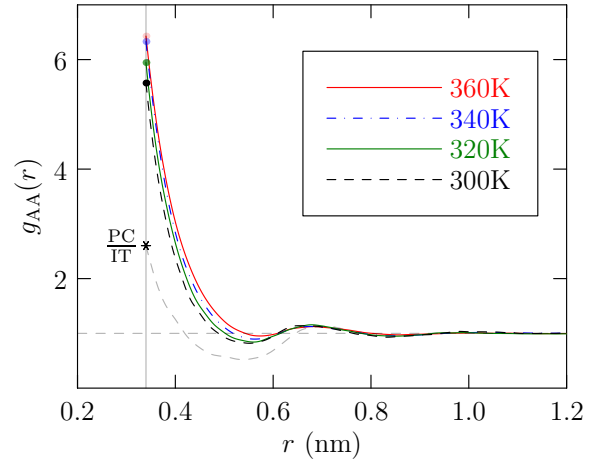


Figure 5: Radial distribution functions for hard-sphere solutes in liquid water at  $p = 1 \text{ atm}$ , and four different temperatures. The spheres have van der Waals radius of 0.17 nm and distance-of-closest-approach to a water oxygen atom of 0.31 nm. The prediction of the information theory (IT) model<sup>44,55</sup> at  $T = 300 \text{ K}$  is shown by the star and the gray dashed curve. The contact value obtained matches the Pratt-Chandler theory numerical result,<sup>53</sup> and is labeled  $\frac{PC}{IT}$ .

# Multi-Solute/Water Simulations to Assess Hydrophobic Interactions

Here we discuss results from another assessment of hydrophobic interactions, namely, simulation of water with multiple hydrophobic solutes sufficiently aggressive that they encounter each other enough to permit thermodynamic analysis of their interactions.<sup>40</sup>

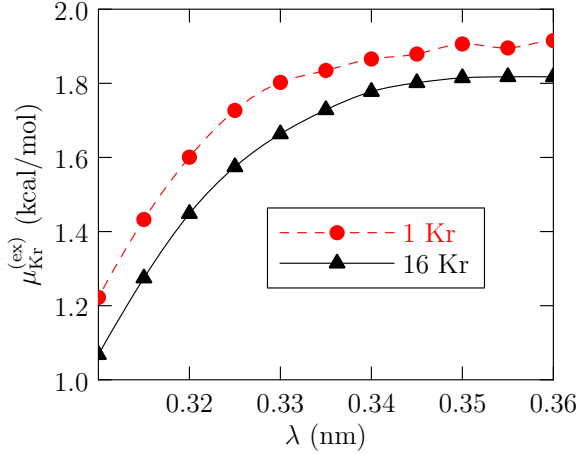


Figure 6: Evaluations of hydration free energies on the basis of quasi-chemical theory for a range of inner-shell boundaries ( $0.31 \text{ nm} < \lambda < 0.36 \text{ nm}$ ) for two Kr concentrations.  $\mu_{\text{Kr}}^{(\text{ex})}$  becomes insensitive in the range  $0.34 \text{ nm} < \lambda < 0.36 \text{ nm}$ . The experimental value is  $1.66 \text{ kcal/mol}$ .<sup>56</sup>

We will use molecular quasi-chemical theory (QCT) as our thermodynamic analysis tool.<sup>30</sup> Results for two simulations, single Kr and multi-Kr, show that the multi-Kr results for hydration free energy,  $\mu_{\text{Kr}}^{(\text{ex})}$ , are distinctly lower (FIG. 6). This already indicates that the hydrophobic interactions are attractive, *i.e.*, favorable. The significant difference derives from slight reduction of the unfavorable packing contribution identified by quasi-chemical theory. Two distinct further analyses then arrive at concordant estimates of the osmotic second virial coefficient  $B_2 \approx -60 \text{ cm}^3/\text{mol}$  (attractive). Beyond the quasi-chemical theory thermodynamic analysis, the observed Kr-Kr distributions were also analyzed with the extrapolation procedure of Krüger, *et al.*<sup>57,58</sup> This approach provides a convenient, theoretically neutral route to the evaluations of  $B_2$  noted below.

Some thirty years ago, a focused molecular-dynamics study<sup>59</sup> estimated  $B_2$  for Kr(aq) to be repulsive (positive). Differences of the models treated and computational resources available probably explain the difference of that previous evaluation with the present work.

## LMF/EXP Theory for Inclusion of Solute Dispersion Interactions for Ar Pair Hydrophobic Interactions

With the hard-sphere results of FIGs. 1 and 5, we proceed further to discuss hydrophobic interactions involving further realistic interactions. Interactions  $u_{\text{AO}}$  and  $u_{\text{AA}}$  are presented for analysis with  $\text{A}=\text{Ar}$  in the example above, and here we consider solute interactions of Lennard-Jones type. As usual,<sup>60</sup> these interactions are separated into a reference part that describes all the repulsive forces,  $u^{(0)}$ , and a remainder  $u^{(1)}$ . We suppose that results corresponding to the reference system are separately available, *e.g.*, from direct numerical simulation such as FIG. 7. Then

$$-\ln \left[ \frac{g_{\text{ArAr}}(r)}{g_{\text{ArAr}}^{(0)}(r)} \right] \approx \beta u_{\text{ArAr}}^{(1)}(r) + \int h_{\text{ArO}}(r') \rho_{\text{O}} \beta u_{\text{OAr}}^{(1)}(|r' - r|) dr'. \quad (3)$$

is the simple theory to be tested. That theory is known as local molecular field theory (LMF).<sup>61</sup> The first term on the right of Eq. (3) builds-in the direct Ar-Ar attractive forces. The second term supplies mean attractive forces from interaction of the solvent with the solute. With  $h_{\text{ArO}} = g_{\text{ArO}} - 1$  conveniently taken from routine simulation (FIG. 1), Eq. (3) is set so that the radial distribution functions on the left of Eq. (3) each approach one (1) at large separation.

A concise rederivation<sup>20</sup> of the approximate Eq. (3) emphasizes the basic concepts of the van der Waals theories of liquids, and is persuasive on that basis. The corresponding theory for



$h_{\text{ArO}}(r)$  is

$$-\ln \left[ \frac{g_{\text{ArO}}(r)}{g_{\text{ArO}}^{(0)}(r)} \right] \approx \beta u_{\text{OAr}}^{(1)}(r) + \int h_{\text{OO}}(r') \rho_{\text{O}} \beta u_{\text{OAr}}^{(1)}(|r' - r|) dr', \quad (4)$$

with  $h_{\text{OO}}(r)$  the observed OO correlation function for pure water. Acknowledging closure approximations specific to traditional implementations, this is just the EXP approximation<sup>62</sup> applied to this correlation problem long ago.<sup>63,64</sup>

The functions  $u_{\text{AO}}$  and  $u_{\text{AA}}$  are distinct, and the interesting possibilities of Eq. (3) lie in how  $u_{\text{AO}}$  and  $u_{\text{AA}}$  contributions balance. In the present application, these contributions balance closely in the relevant regime of separations (FIG. 7), predicting small changes due to this balanced inclusion of attractive interactions. Nevertheless, the observed differences  $g_{\text{ArAr}}(r)$  and  $g_{\text{ArAr}}^{(0)}(r)$  are large in contact geometries (FIG. 7).

In this application, finally, we are forced again to the conclusions that attractive interactions lead to substantial changes in the hydrophobic interactions, and that the approximation Eq. (3) does not describe those changes well here. Work of long ago arrived at different conclusions because accurate results for the reference system (FIGs. 5 and 7) were not available for this analysis.

The second osmotic virial coefficient,  $B_2$ , becomes more attractive with increasing temperature below  $T = 360$  K (FIG. 8). This behavior is consistent with important recent results of Koga<sup>39</sup> and of Ashbaugh, *et al.*<sup>41</sup> With attractive interactions in play,  $B_2$  can change from positive to negative values with increasing temperatures. This is consistent also with historical work<sup>59</sup> that  $B_2 \approx 0$  for intermediate cases.

## Discussion

Changing purely repulsive atomic interactions to include realistic attractions *weakens* primitive hydrophobic bonds (FIG. 7). According to the LMF/EXP theory,<sup>21,63</sup> the hydration environment competes with direct Ar-Ar attractive interactions (Eq. (3)). The outcome of that competition is sensitive to the differing strengths of the attrac-

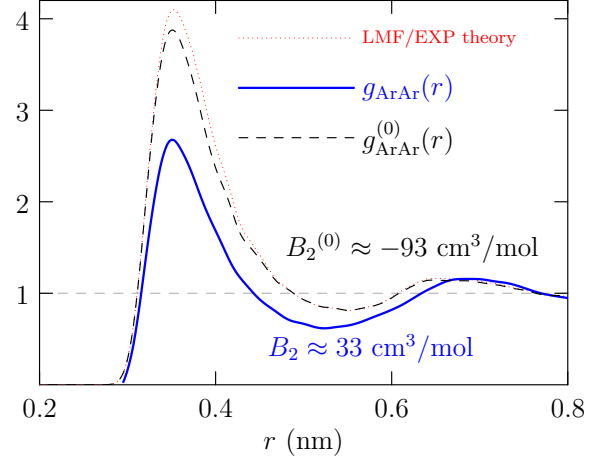


Figure 7: For  $T = 300$  K, comparison of  $g_{\text{ArAr}}(r)$  (blue-solid) to the result for the reference system  $g_{\text{ArAr}}^{(0)}(r)$  (LJ repulsions, black-dashed) and the LMF/EXP approximation (red-dotted). Solute attractive forces reduce the contact pair correlations and thus weaken hydrophobic bonds. Note also the significantly different behavior of  $g_{\text{ArAr}}^{(0)}(r)$  and  $g_{\text{ArAr}}(r)$  in the *second shell*. Those differences suggest more basic structural changes driven by attractive interactions.

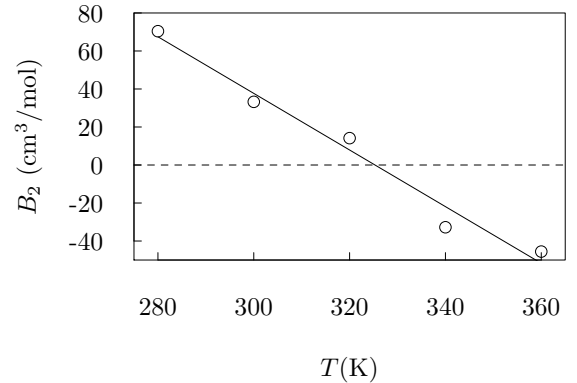


Figure 8: Numerical values of the osmotic second virial coefficients,  $B_2$ , obtained from the radial distribution functions using the extrapolation procedure of Krüger, *et al.*,<sup>57,58</sup> are nicely consistent with important recent results of Koga<sup>39</sup> and of Ashbaugh, *et al.*<sup>41</sup>

tive interactions. The earlier application<sup>63</sup> used the EXP approximation to analyze the available Monte Carlo calculations on atomic LJ solutes in water.<sup>43</sup> That theoretical modeling found modest effects of attractive interactions, and encouraging comparison with the Monte Carlo results. This application of the LMF theory (Eq. (3)) again predicts modest effects of attractive interactions, but the net comparison from the simulation results shows big differences. The alternative outcome is due to the fact that the earlier application used the PC theory for the reference system  $g_{\text{ArAr}}^{(0)}(r)$ . We now know that approximation is not accurate here,<sup>22</sup> despite being the only theory available. Here the LMF theory (Eq. (3)) predicts modest-sized changes, also opposite in sign to the observed changes. Note further that  $g_{\text{ArAr}}^{(0)}(r)$  and  $g_{\text{ArAr}}(r)$  differ distinctively in the second hydration shell, and those differences suggest more basic structural changes driven by attractive interactions.

Earlier theoretical studies featured  $\langle \epsilon | r, n_\lambda = 0 \rangle$ , a central object in QCT for the present problem.<sup>21</sup> A more accurate evaluation would involve  $n$ -body ( $n > 2$ ) correlations, even if treated by superposition approximations.<sup>65</sup> Detailed treatment of the Ar<sub>2</sub> diatom geometry is the most prominent difference between that QCT approach and the present LMF theory (Eq. (3)). Nevertheless, a full QCT analysis of these differences is clearly warranted and should be the subject of subsequent study.

Finally, since attractions make large, masking contributions, tests of the PC theory<sup>43,44</sup> against results with realistic attractive interactions should address the role of attractive interactions, which were not included in the PC theory.

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## References

- (1) Chan, D. Y. C.; Mitchell, D. J.; Ninnham, B. W.; Pailthorpe, B. A. In *Recent Advances*; Franks, F., Ed.; WATER: A COMPREHENSIVE TREATISE; Plenum: New York, 1979; Vol. 6; pp 239–278.
- (2) Franks, F. In *Aqueous Solutions of Amphiphiles and Macromolecules*; Franks, F., Ed.; WATER: A COMPREHENSIVE TREATISE; Springer, 1975; Vol. 4; pp 1–94.
- (3) Tucker, E. E.; Christian, S. D. A Prototype Hydrophobic Interaction. The Dimerization of Benzene in Water. *J. Phys. Chem.* **1979**, *83*, 426–427.
- (4) Rossky, P. J.; Friedman, H. L. Benzene-Benzene Interaction in Aqueous Solution. *J. Phys. Chem.* **1980**, *84*, 587–589.
- (5) Pratt, L. R. Theory of Hydrophobic Effects. *Ann. Rev. Phys. Chem.* **1985**, *36*, 433–449.
- (6) Pratt, L. Molecular Theory of Hydrophobic Effects: "She is too mean to have her name repeated". *Ann. Rev. Phys. Chem.* **2002**, *53*, 409–436.
- (7) Berne, B. J.; Weeks, J. D.; Zhou, R. Dewetting and Hydrophobic Interaction in Physical and Biological Systems. *Ann. Rev. Phys. Chem.* **2009**, *60*, 85–103.
- (8) Kumar, A.; Biebuyck, H. A.; Whitesides, G. M. Patterning Self-Assembled Monolayers: Applications in Materials Science. *Langmuir* **1994**, *10*, 1498–1511.
- (9) De Vos, R. M.; Maier, W. F.; Verweij, H. Hydrophobic Silica Membranes for Gas Separation. *J. Memb. Sci.* **1999**, *158*, 277–288.
- (10) Giessler, S.; Diniz da Costa, J.; Lu, M. *Hydrophobic Microporous Silica Membranes for Gas Separation and Membrane Reactors*,

4th ed.; Imperial College Press, 2004; pp 237–262.

- (11) Guo, Z.; Zhou, F.; Hao, J.; Liu, W. Stable Biomimetic Super-Hydrophobic Engineering Materials. *J. Am. Chem. Soc.* **2005**, *127*, 15670–15671.
- (12) Cygan, R.; Brinker, C.; Nyman, M.; Leung, K.; Rempe, S. B. A molecular basis for advanced materials in water treatment. *MRS Bulletin* **2008**, *33*, 42–47.
- (13) Barkhudarov, P. M.; Shah, P. B.; Watkins, E. B.; Doshi, D. A.; Brinker, C. J.; Majewski, J. Corrosion inhibition using superhydrophobic films. *Corrosion Science* **2008**, *50*, 897–902.
- (14) Clawson, J. S.; Cygan, R. T.; Alam, T. M.; Leung, K.; Rempe, S. B. Ab initio study of hydrogen storage in water clathrates. *J. Comput. Theor. Nanosci.* **2010**, *7*, 2602–2606.
- (15) Aman, A. M.; Koh, C. A. Interfacial phenomena in gas hydrate systems. *Chem. Soc. Rev.* **2016**, *45*, 1678–1690.
- (16) Richards, F. M. Areas, Volumes, Packing, and Protein Structure. *Ann. Rev. Biophys. Bioeng.* **1977**, *6*, 151–176.
- (17) Richards, F. M. The Protein Folding Problem. *Scientific American* **1991**, *264*, 54.
- (18) Tanford, C. The Hydrophobic Effect and the Organization of Living Matter. *Science* **1978**, *200*, 1012–1018.
- (19) Pohorille, A.; Pratt, L. R. Is Water the Universal Solvent for Life? *Origins of Life and Evolution of Biospheres* **2012**, *42*, 405–409.
- (20) Chaudhari, M. I.; Rempe, S. B.; Asthagiri, D.; Tan, L.; Pratt, L. R. Molecular Theory and the Effects of Solute Attractive Forces on Hydrophobic Interactions. *J. Phys. Chem. B* **2016**, *120*, 1864–1870.
- (21) Asthagiri, D.; Merchant, S.; Pratt, L. R. Role of Attractive Methane-Water Interactions in the Potential of Mean Force between Methane Molecules in Water. *J. Chem. Phys.* **2008**, *128*, 244512.
- (22) Chaudhari, M. I.; Holleran, S. A.; Ashbaugh, H. S.; Pratt, L. R. Molecular-scale Hydrophobic Interactions between Hard-Sphere Reference Solutes are Attractive and Endothermic. *Proc. Nat. Acad. Sci. USA* **2013**, *110*, 20557–20562.
- (23) Pratt, L. R.; Pohorille, A. In *Proceedings of the EBSA 1992 International Workshop on Water-Biomolecule Interactions*; Palma, M. U., Palma-Vittorelli, M. B., Parak, F., Eds.; Società Italiana de Fisica: Bologna, 1993; pp 261–268.
- (24) Chaudhari, M. I. Molecular Simulations to Study Thermodynamics of Polyethylene Oxide Solutions. Ph.D. thesis, Department of Chemical & Biomolecular Engineering, Tulane University, 2013.
- (25) Kirchner, B.; Hutter, J.; Kuo, I.-F. W.; Mundy, C. J. Hydrophobic hydration from Carr-Parrinello simulations. *Int. J. Mod. Phys. B* **2004**, *18*, 1951.
- (26) Sabo, D.; Rempe, S. B.; Greathouse, J. A.; Martin, M. G. Molecular studies of the structural properties of hydrogen gas in bulk water. *Mol. Simul.* **2006**, *32*, 269–278.
- (27) Sabo, D.; Varma, S.; Martin, M. G.; Rempe, S. B. Studies of the thermodynamic properties of hydrogen gas in bulk water. *J. Phys. Chem. B* **2008**, *112*, 867–876.
- (28) Śmiechowski, M. Molecular hydrogen solvated in water – A computational study. *J. Chem. Phys.* **2015**, *143*, 244505.
- (29) Jiao, D.; Rempe, S. B. CO<sub>2</sub> solvation free energy using quasi-chemical theory. *J. Chem. Phys.* **2011**, *134*, 224506.
- (30) Rogers, D. M.; Jiao, D.; Pratt, L. R.; Rempe, S. B. Structural Models and Molecular Thermodynamics of Hydration of Ions and Small Molecules. *Ann. Rep. Comp. Chem.* **2012**, *8*, 71–127.



- (31) Pratt, L. R.; Garde, S.; Hummer, G. Theories of Hydrophobic Effects and the Description of Free Volume in Complex Liquids. *NATO ADVANCED SCIENCE INSTITUTES SERIES, SERIES C, MATHEMATICAL AND PHYSICAL SCIENCES* **1999**, 529, 407–420.
- (32) Ashbaugh, H. S.; Pratt, L. R. Contrasting Nonaqueous against Aqueous Solvation on the Basis of Scaled-Particle Theory. *J. Phys. Chem. B* **2007**, 111, 9330–9336.
- (33) Chaudhari, M. I.; Pratt, L. R.; Paulaitis, M. E. Communication: Direct Observation of a Hydrophobic Bond in Loop Closure of a Capped (–OCH<sub>2</sub>CH<sub>2</sub>)<sub>n</sub> oligomer in water. *J. Chem. Phys.* **2010**, 133, 231102.
- (34) Chaudhari, M. I.; Pratt, L. R. In *OIL SPILL REMEDIATION: COLLOID CHEMISTRY-BASED PRINCIPLES AND SOLUTIONS*; Somasundaran, P., Farinato, R., Patra, P., Papadopoulos, K. D., Eds.; John Wiley and Sons, Inc., 2012; See also: arXiv:1208.0349v2.
- (35) Tsige, M.; Soddemann, T.; Rempe, S. B.; Grest, G. S.; Kress, J. D.; Robbins, M. O.; Sides, S. W.; Stevens, M. J.; Webb, E. Interactions and structure of poly(dimethylsiloxane) at silicon dioxide surfaces: Electronic structure and molecular dynamics studies. *J. Chem. Phys.* **2003**, 118, 5132.
- (36) Weikl, T. R. Loop-closure Principles in Protein Folding. *Arch. Biochem. Biophys.* **2008**, 469, 67–75.
- (37) Chaudhari, M.; Pratt, L.; Paulaitis, M. E. Loop-Closure and Gaussian Models of Collective Structural Characteristics of Capped PEO Oligomers in Water. *J. Phys. Chem. B* **2014**, 119, 8863–8867.
- (38) Kumar, S.; Rosenberg, J. M.; Bouzida, D.; Swendsen, R. H.; Kollman, P. A. The weighted histogram analysis method for free-energy calculation on biomolecules . I. The method. *J. Comp. Chem.* **1992**, 13, 1011–1021.
- (39) Koga, K.; Widom, B. Thermodynamic Functions as Correlation-Function Integrals. *J. Chem. Phys.* **2013**, 138, 114504.
- (40) Chaudhari, M. I.; Sabo, D.; Pratt, L. R.; Rempe, S. B. Hydration of Kr(aq) in Dilute and Concentrated Solutions. *J. Phys. Chem. B* **2015**, 119, 9098–9102.
- (41) Ashbaugh, H. S.; Weiss, K.; Williams, S. M.; Meng, B.; Surampudi, L. N. Temperature and Pressure Dependence of Methane Correlations and Osmotic Second Virial Coefficients in Water. *J. Phys. Chem. B* **2015**, 119, 6280–6294.
- (42) Asthagiri, D.; Merchant, S.; Pratt, L. R. Role of Attractive Methane-Water Interactions in the Potential of Mean Force between Methane Molecules in Water. *J. Chem. Phys.* **2008**, 128, 244512.
- (43) Pangali, C.; Rao, M.; Berne, B. J. A Monte Carlo Simulation of the Hydrophobic Interaction. *J. Chem. Phys.* **1979**, 71, 2975–2981.
- (44) Hummer, G.; Garde, S.; García, A. E.; Pohorille, A.; Pratt, L. R. An Information Theory Model of Hydrophobic Interactions. *Proc. Natl. Acad. Sci. USA* **1996**, 93, 8951–8955.
- (45) Garde, S.; Hummer, G.; García, A. E.; Paulaitis, M. E.; Pratt, L. R. Origin of Entropy Convergence in Hydrophobic Hydration and Protein Folding. *Phys. Rev. Letts.* **1996**, 77, 4966–4968.
- (46) Pratt, L. R.; Pohorille, A. Hydrophobic Effects and Modeling of Biophysical Aqueous Solution Interfaces. *Chem. Rev.* **2002**, 102, 2671–2692.
- (47) Pratt, L. R.; Pohorille, A.; Asthagiri, D. What Is Special About Water as a Matrix Of Life? *arXiv preprint physics/0701282* **2007**,
- (48) Pierotti, R. A. A Scaled Particle Theory of Aqueous and Nonaqueous Solutions. *Chem. Rev.* **1976**, 76, 717–726.

- (49) Stillinger, F. H. Structure in Aqueous Solutions of Nonpolar Solutes from the Standpoint of Scaled-Particle Theory. *J. Soln. Chem.* **1973**, 2, 141–158.
- (50) Gomez, M. A.; Pratt, L. R.; Hummer, G.; Garde, S. Molecular Realism in Default Models for Information Theories of Hydrophobic Effects. *J. Phys. Chem. B* **1999**, 103, 3520–3523.
- (51) Ashbaugh, H.; Pratt, L. Colloquium: Scaled Particle Theory and the Length Scales of Hydrophobicity. *Rev. Mod. Phys.* **2006**, 78, 159–178.
- (52) Hill, T. L. *An Introduction to Statistical Thermodynamics*; Addison-Wesley: Reading MA USA, 1960.
- (53) Pratt, L. R.; Chandler, D. Theory of the Hydrophobic Effect. *J. Chem. Phys.* **1977**, 67, 3683–3704.
- (54) Mancera, R. L.; Buckingham, A. D.; Skipper, N. T. The Aggregation of Methane in Aqueous Solution. *J. Chem. Soc. Faraday Trans.* **1997**, 93, 2263–2267.
- (55) Hummer, G.; Garde, S.; García, A. E.; Paulaitis, M. E.; Pratt, L. R. The Pressure Dependence of Hydrophobic Interactions is Consistent with the Observed Pressure Denaturation of Proteins. *Proc. Nat. Acad. Sci. USA* **1998**, 95, 1552–1555.
- (56) Young, C. *Hydrogen and Deuterium (Solubility data series)*; Pergamon Press, 1981.
- (57) Krüger, P.; Schnell, S. K.; Bedeaux, D.; Kjelstrup, S.; Vlugt, T. J.; Simon, J.-M. Kirkwood–Buff Integrals for Finite Volumes. *J. Phys. Chem. Letts.* **2012**, 4, 235–238.
- (58) Schnell, S. K.; Englebienne, P.; Simon, J.-M.; Krüger, P.; Balaji, S. P.; Kjelstrup, S.; Bedeaux, D.; Bardow, A.; Vlugt, T. J. How to apply the Kirkwood–Buff Theory to Individual Species in Salt Solutions. *Chem. Phys. Letts.* **2013**, 582, 154–157.
- (59) Watanabe, K.; Andersen, H. C. Molecular-Dynamics Study of the Hydrophobic Interaction in an Aqueous-Solution of Krypton. *J. Phys. Chem.* **1986**, 90, 795–802.
- (60) McQuarrie, D. *Statistical Mechanics*; University Science Books: California, 2000.
- (61) Rodgers, J. M.; Weeks, J. D. Local molecular field theory for the treatment of electrostatics. *J. Phys.: Condens. Matter* **2008**, 20.
- (62) Hansen, J.-P.; McDonald, I. R. *Theory of Simple Liquids*; Academic Press, 1976.
- (63) Pratt, L. R.; Chandler, D. Effects of Solute-Solvent Attractive Forces on Hydrophobic Correlations. *J. Chem. Phys.* **1980**, 73, 3434–3441.
- (64) Hummer, G.; Garde, S. Cavity Expulsion and Weak Dewetting of Hydrophobic Solutes in Water. *Phys. Rev. Lett.* **1998**, 80, 4193–4196.
- (65) Ashbaugh, H. S.; Pratt, L. R.; Paulaitis, M. E.; Clohery, J.; Beck, T. L. Deblurred Observation of the Molecular Structure of an Oil-Water Interface. *J. Am. Chem. Soc.* **2005**, 127, 2808–2809.